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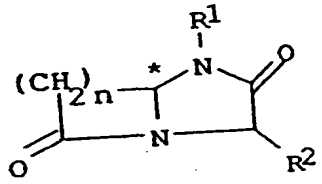
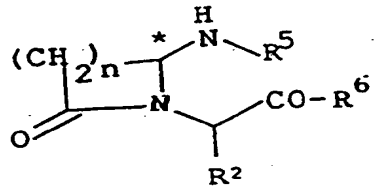
(54) Title: PROCESS FOR THE PREPARATION OF CONDENSED IMIDAZOLES



(I)



(II)

(57) Abstract

A process for the preparation of compounds of formula (I), wherein $R^1$ represents hydrogen, $C_{1-4}$ alkyl, $CHR^3CO$ or $CHR^3COOR^4$ in which $R^3$ and $R^4$ each independently represent hydrogen or $C_{1-4}$alkyl; $R^2$ represents hydrogen alkyl; and n is an integer 2, 3 or 4; which process comprises cyclising a compound of formula (II), wherein $R^2$ and n defined in relation to formula (I); $R^5$ represents hydrogen or a group $COOR^7$ wherein $R^7$ is a $C_{1-4}$ alkyl group or a group; and $R^6$ represents a hydroxy group or a group $OR^8$ wherein $R^8$ represents $C_{1-6}$ alkyl or a benzyl group; and ter, as necessary, carrying out one more of the following steps: i) removing any protecting group; and ii) converting pound of formula (I) into another compound of formula (I).

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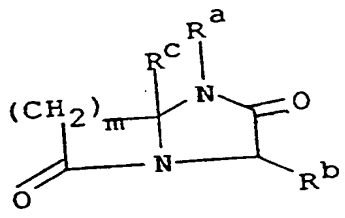
# Process for the preparation of condensed imidazoles

The invention relates to a process for preparing certain fused imidazole derivatives and in particular for preparing chiral fused imidazole derivatives.

European Patent Application, Publication No. 0,335,483 discloses certain fused imidazole derivatives of formula (A):



wherein,

$R^a$ is hydrogen, $C_{1-4}$ alkyl, $CHR^dCONHR^e$ or $CHR^dCOOR^e$ in which $R^d$ and $R^e$ are each hydrogen or $C_{1-4}$ alkyl;

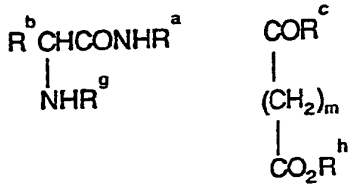
$R^b$ is hydrogen, $C_{1-5}$ alkyl or any residue $R^b$ of an amino acid $R^bCH(NH_2)COOH$

$R^c$ is hydrogen, $C_{1-4}$ alkyl, $CONH_2$ or $CO_2R^f$ in which $R^f$ is hydrogen or $C_{1-4}$ alkyl; and

m is 2, 3 or 4.

EP 0,335,483 also discloses a process for preparing the compounds of formula (A) which involves either:

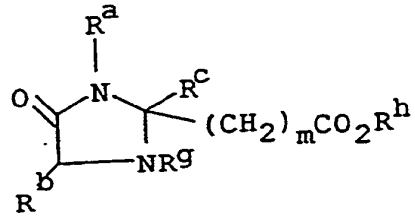
a) reacting a compound of formula (B) with a compound of formula (C):



(B) (C)

wherein $R^a$, $R^b$, $R^c$, and m are as defined in relation to formula (A), $R^g$ is hydrogen and $R^h$ is hydrogen, $C_{1-4}$ alkyl or benzyl; or

b) cyclising a compound of formula (D):



(D)

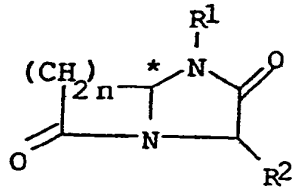
where in $R^a$, $R^b$, $R^c$ and m are as defined in relation to formula (A) and $R^g$ and $R^h$ are as defined in relation to formulae (B) and (C).

The compounds of formula (A) are disclosed in EP 0,335,483 as having activity as nootropic reagents.

EP 0,335,483 also discloses that the compounds of formula (A) can contain one or more chiral carbons. In particular it is to be noted that the bridgehead carbon of formula (A) is always a chiral carbon.

A process has now been discovered which facilitates the preparation of certain compounds of formula (A) and in particular facilitates the preparation of individual optical isomers of such compounds in which the chiral carbon is the bridgehead carbon.

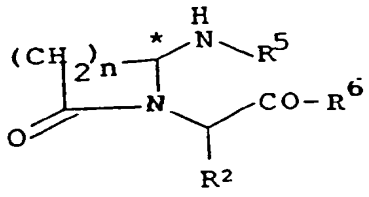
Accordingly, the present invention provides a process for the preparation of compounds of formula (I):



(I)

wherein
$R^1$ represents hydrogen, $C_{1-4}$ alkyl, $CHR^3CONHR^4$ or $CHR^3COOR^4$ in which $R^3$ and $R^4$ each independently represent hydrogen or $C_{1-4}$ alkyl;
$R^2$ represents hydrogen or $C_{1-5}$ alkyl; and n is an integer 2, 3 or 4;

which process comprises cyclising a compound of formula (II):



(II)

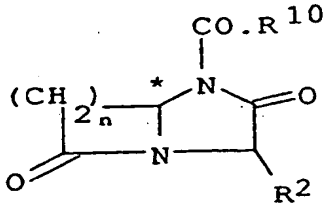
wherein $R^2$ and n are as defined in relation to formula (I);
$R^5$ represents hydrogen or a group $COOR^7$ wherein $R^7$ is a $C_{1-4}$ alkyl group or a benzyl group; and $R^6$ represents a hydroxy group or a group $OR^8$ wherein $R^8$ represents $C_{1-6}$ alkyl or a benzyl group; and thereafter, as necessary, carrying out one or more of the following steps:

i) removing any protecting group; and

ii) converting a compound of formula (I) into another compound of formula (I).

Suitably the cyclisation is effected by a cyclising reagent.

In certain circumstances, the cyclisation of the compound of formula (II) may provide a compound of formula (III):



(III)

wherein $R^2$ and n are as defined in relation to formula (I) and $R^{10}$ is a $C_{1-6}$ alkyl group or a group $OR^7$ wherein $R^7$ is as defined in relation to formula (II); the compound of formula (III) may then be converted into a compound of formula (I), wherein $R^1$ is H, by hydrogenolysis or hydrolysis, the resulting compound of formula (I) may subsequently be converted into other compounds of formula (I) as desired.

Compound (III) is generally provided when the cyclising reagent is a carboxylic anhydride.

Accordingly, the present invention, in a further particular aspect provides a process for preparing a compound of formula (I), which process comprises hydrogenolysing or hydrolysing a compound of the above defined formula (III); and thereafter, as necessary converting the resulting compound of formula (I), wherein $R^1$ is H, into a further compound of formula (I).

When $R^6$ is OH, the cyclisation of a compound of formula (II) is conveniently effected under dehydration cyclisation conditions, preferably in the presence of a dehydration cyclisation reagent.

Suitable dehydration cyclisation reagents include dicyclohexylcarbodiimide or carboxylic anhydrides such as acetic anhydride.

When the reagent is dicyclohexylcarbodiimide, the reaction is preferably carried out in the presence of an organic base such as triethylamine, in any suitable solvent, such as acetonitrile, at any convenient temperature providing a suitable rate of formation of the required product, aptly at ambient temperature.

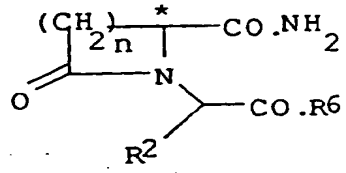
When the reagent is a carboxylic anhydride such as acetic anhydride, the reaction may be carried out in any suitable solvent, but conveniently using acetic anhydride itself as solvent, and at any convenient temperature providing a suitable rate of formation of the product, suitably at the reflux temperature of the solvent and preferably in the presence of anhydrous sodium acetate.

Suitable means for hydrogenolysing any compound of formula (III) include conventional catalytic hydrogenolysis techniques. Suitable means for hydrolysing any compound include conventional hydrolysis techniques, such as mild acid hydrolysis, for example by using an acidic resin such as Amberlite IR 120.

When $R_6$ is a group $OR_8$, the cyclisation is preferably effected by use of a strong base such as n-butyl lithium or potassium t-butoxide.

The cyclisation of a compound of formula (II), wherein $R_6$ is a group $OR_8$, may be suitably carried out in an aprotic solvent, such as tetrahydrofuran or toluene: for example when potassium t-butoxide is the strong base the reaction is conveniently carried out in toluene, at ambient temperatures: when n-butyl lithium is the strong base the reaction is conveniently carried out in tetrahydrofuran at low to ambient temperature, generally at a temperature within the range of from -80°C to -30°C, for example in the range of from -70 to -65°C.

A compound of the abovedefined formula (II), may be prepared by reacting a compound of formula (IV):



(IV)

wherein $R^2$, $R^6$ and n are as defined in relation to formula (II), with a reagent capable of converting a $-CO.NH_2$ group into an $-NH_2$ group, and thereafter, if required, carrying out one or more of the following optional steps:

i) protecting and thereafter, as necessary, de-protecting any group;

ii) converting a compound wherein $R^5$ is H into a compound wherein $R^5$ is $COOR^7$, wherein $R^7$ is as defined in relation to formula (II); and

iii) converting any group $R^6$ which represents $OR^8$ into a group $R^6$ which represents hydroxy.

Suitable reagents capable of converting a $-CO.NH_2$ group into an $-NH_2$ group include bis(trifluoroacetoxy)iodosobenzene or a source of hypochlorite ion, such as sodium hypochlorite.

The conditions for the reaction between the compound of formula (IV) and the reagent capable of converting a $-CO.NH_2$ group into an $-NH_2$ group will of course depend upon the particular reagent used, but generally the appropriate conventional conditions for the particular reagent chosen will be used: when the reagent is bis(trifluoro- acetoxy)iodosobenzene the reaction is carried out in any suitable solvent, such as aqueous acetonitrile, preferably in an inert atmosphere such as nitrogen, at any convenient temperature which provides a suitable rate of formation of the desired product, conveniently at a low to ambient temperature, for example in the range of from 0°-5°C: when the reagent is a source of hypochlorite ions, such as sodium hypochlorite, the reaction is carried out in any suitable solvent, generally an aqueous solvent, conveniently water, at any convenient temperature providing a suitable rate of formation of the required product, such as in the range of 0°C to 100°C, generally in the range of from 0°C to room temperature, for example 0°C to 5°C; preferably the sodium hypochlorite reaction is carried out in the presence of sodium hydroxide.

The conversion of a compound wherein $R^5$ is H into a compound wherein $R^5$ is $COOR^7$ may be carried out using a conventional chemical procedures, for example the conversion of a compound wherein $R^5$ is H into a compound wherein $R^5$ is $COOR^7$ is provided by treating the appropriate compound with a compound of formula (V):

$$X\text{-}CO.OR^7 \qquad (V)$$

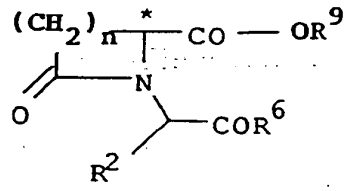
wherein $R^7$ is as defined in relation to formula (II) and X represents a leaving group, such as a halogen atom, for example a chlorine atom. Usually, the appropriate compound is present in salted from, for example alkali metal salted form, such as a sodium salted form, prepared by treating the appropriate compound with a base, for example an alkali

metal hydroxide, such as sodium hydroxide.

The reaction between the appropriate compound and the compound of formula (V) may be carried out in any suitable solvent, generally an aqueous solvent, conveniently water, at low to medium temperature, generally in the range of 0°C to + 40°C, suitable from 0°C to 5° or from 5°C to ambient temperature.

The conversion of any group $R^6$ which represents $OR^8$ into a group $R^6$ which represents hydroxy may be carried out using the appropriate conventional procedure, for example by using conventional hydrolysis methods, for example treatment with an alkali metal hydroxide, such as sodium hydroxide.

A compound of formula (IV) may be prepared by aminating a compound of formula (VI):



(VI)

wherein $R^2$, $R^6$ and n are as defined in relation to formula (II) and $R^9$ is a $C_{1-6}$ alkyl group; and thereafter, if required,

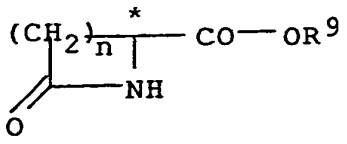
i) protecting and thereafter, as necessary, deprotecting any group;

ii) converting any group $R^6$ which represents $OR^8$ into a group $R^6$ which represents hydroxy.

The amination of compound (VI) may be effected using conventional amination conditions, for example by using concentrated aqueous ammonia at any temperature providing a convenient rate of formation of the required product, conveniently at ambient temperature.

A compound of formula (VI) may be prepared by reacting a compound of

formula (VII):



(VII)

wherein $R^9$ and n are as defined in relation to formula (VI), with a compound of formula (VIII):

$$X\text{-}CH(R^2)CO.R^6 \qquad \text{(VIII)}$$

wherein $R^2$ and $R^6$ are as defined in relation of formula (II) and X is a leaving group such as halide; and thereafter, if required carrying out one or more of the following optional steps:

i) protecting and thereafter, as necessary, de-protecting any group;

ii) converting any group $R^6$ which represents $OR^8$ into a group $R^6$ which represents hydroxy.

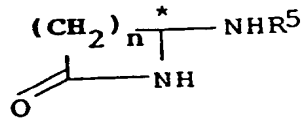
Suitably the compound of formula (VII) is present in an activated form, for example a salted form such as a sodium salted form, provided by treating the compound of formula (VII) with a salting agent such as sodium hydride.

The reaction between a compound of formula (VII) and a compound of formula (VIII) may be carried out using analogous conditions to those described in Berichte, 44, 1333 (1911).

The compounds of formula (VII) are known compounds or they may be prepared by analogous procedures to those used to prepare known compounds, for example the compounds of formula (VII) wherein n is 2 are known, commercially available compounds.

A compound of formula (II) may also be prepared by reacting a compound

of formula (IX):



(IX)

wherein $R^5$ and n are as defined in relation to formula (II), with a compound of the hereinbefore defined formula (VIII); and thereafter, if required, carrying out one or more of the following optional steps:

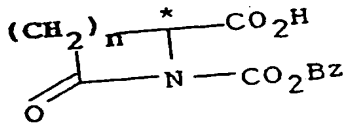
i) protecting and thereafter, as necessary, de-protecting any group;

ii) converting one group $R^5$ into another group $R^5$.

The reaction between the compounds of formulae (VIII) and (IX) may be carried out using conditions analogous to those used in the reaction between compounds of formulae (VII) and (VIII).

The compounds of formula (IX) are known compounds or they may be prepared using methods analogous to those used to prepared known compounds, for example the methods disclosed in Heterocycles, 14, 1245 (1980).

Alternatively, a compound of formula (IX) may be prepared by reacting a compound of formula (X):



(X)

wherein n is as defined in relation to formula (I), with a reagent capable of

converting a carboxyl group into a group -$NHR^5$ and thereafter, as required, carry out one or more of the following optional steps:

i) removing any protecting group, in particular any benzylcarboxylate group;

ii) converting one group $R^5$ into another group $R^5$.

A suitable reagent capable of converting a carboxyl group into a group -$NHR^5$ is diphenylphosphorylazide in the presence of triethylamine and, as required, an appropriate alcohol. The reaction conditions for the reaction between the compound of formula (X) and the reagent capable of converting a carboxyl group into a group -$NHR^5$ will in general be the appropriate conventional conditions for the particular reagent chosen; for example when the reagent is a Curtius reagent such as diphenylphosphorylazide the reaction is suitably effected under the Curtius reaction conditions such as those disclosed in Synthesis, 294 (1985).

An alcohol is generally required when $R^5$ represents a group -$COOR^7$: the particular alcohol required is that dictated by the value of $R^7$ in the required compound of formula (IX): thus the alcohol is an alcohol of formula $R^7OH$.

Protecting groups may be removed using the appropriate conventional procedure, for example a benzyl carboxylate group may be removed using conventional catalytic hydrogenolysis using hydrogen and a Pd/C catalyst.

Suitable conversions of one group $R^5$ into another group $R^5$ include those mentioned hereinbefore.

The compounds of formula (X) are known compounds or they may be prepared in accordance with procedures used to prepare known compounds, for example those disclosed in Synthesis, 294 (1985). In particular it is to be noted that the compounds of formula (X) wherein n is 2 may be prepared by conventional benzylation of the naturally occurring amino acid pyroglutamic acid. The R and S isomers of pyroglutamic acid are readily available in resolved form.

Suitable protecting groups for any of the groups mentioned herein and methods for removing such protecting groups are those used conventionally in the art, for example a suitable amino protecting group is the group $COR^{10}$ as defined above.

The preparation of a resolved form ((R) or (S)) isomer of a compound of formula (I) may suitably be obtained by the sequence of reactions summarised below in Schemes 1 to 5:

**Scheme (1)**

(II) → (I)

**Scheme (2):**

(II) → (III) → (I)

**Scheme (3):**

(VII) → (VI) → (IV) → (II) → (I)

**Scheme (4):**

(VII) → (VI) → (IV) → (II) → (III) → (I)

**Scheme (5):**

(X) → (IX) → (II) → (II) → (I)

In the abovementioned schemes the compounds of formulae (I), (II, (III), (IV), (VI), (VII), (IX) and (X) are as defined above and the reaction conditions for each reaction are as defined hereinbefore.

Each of the abovementioned Schemes (1), (2), (3), (4) and (5) form a further specific aspect of the present invention.

In Schemes (1) and (3) it is particularly advantageous if the cyclisation of

(II) to (I) is effected using dicyclohexylcarbodiimide.

In Schemes (2), (4) and (5) it is particularly advantageous if the cyclisation of (II) to (III) is effected using a carboxylic anhydride.

In Scheme (4) it is particularly advantageous if variable $R^6$ in the compounds of formulae (VI) and (IV) is -O-t-butyl.

The following Examples illustrate the present invention but do not limit it in any way.

**Example 1**

**(R,S)-5-Benzyloxycarbonylamino-2-pyrrolidinone**

A mixture of 5-ethoxy-2-pyrrolidinone (20 g) and benzyl carbamate (25.8 g) were stirred at 85°C until fusion. A catalytic amount of 4-toluenesulfonic acid was added and stirring at 85°C was continued for six hours, while distilling off the ethanol formed.

After cooling, the reaction mixture was chromatographed over silica gel (dichloromethane - methanol 95:5) to yield 26.7 g of the title compound, as a white solid melting at 90-92°C.

**$^1$H-NMR (DMSO-$d_6$ delta**: 8.10 (bs; 1H; CONH); 7.90 (bd; J = 9Hz, 1H, CHNHCO); 7.35 (s; 5H, Ph); 5.20 (c.a.; 1H, CH); 5.05 (s; 2H, $\underline{CH_2}$Ph); 2.50 - 1.50 (c.a.; 4H, $\underline{CH_2}CH_2$).

**MS (E.I., 70 eV), m/z**: 234 (M+.), 190 (M-$CO_2$), 150 (M-$C_4H_6NO$), 143 (M-$C_7H_7$), 128 (M-$C_7H_6O$), 108 ($C_7H_8O$), 91 ($C_7H_7$), 84 ($C_4H_6NO$).

**Example 2**

**Ethyl (R,S)-5-benzyloxycarbonylamino-2-oxo-1-pyrrolidine-acetate**

To an ice cold solution of (R,S)-5-benzyloxycarbonylamino-2-pyrrolidinone (8 g) in acetonitrile (400 ml), sodium hydride (55-60% oil dispersion) (1.5 g) was added portionwise. Stirring was continued for 1 hour, then a solution of ethyl bromoacetate (6.3 g) in acetonitrile was added dropwise, keeping the internal temperature between 0 and 5°C.

After stirring for 4 hours at room temperature, the reaction mixture was heated at 50°C for 1 hour. The solvent was removed under vacuum and the residue was partitioned between ethyl acetate and water. The organic layer was washed with a saturated solution of sodium hydrogen carbonate and water, dried ($Na_2SO_4$) and evaporated under vacuum to give 9 g of the title compound, as an oil, Rf = 0.33 (silica gel plates, dichloromethane -

methanol 95:5).

**$^1$H-NMR ($CDCl_3$), delta:** 7.35 (s, 5H, Ph); 5.85 (bd, J = 8.5Hz, 1H, NH); 5.50 (c.a., 1H, CH); 5.10 (s, 2H, $\underline{CH_2}Ph$); 4.15 (q, J = 7.5Hz, 2H, $\underline{CH_2}CH_3$); 4.10 and 3.95 (ABq, J = 14Hz, 2H, $NH\underline{CH_2}CO$); 2.75-1.75 (c.a., 4H, $CH_2CH_2$); 1.22 (t, J = 7.5Hz, 3H, $CH_2\underline{CH_3}$).

**MS (E.I., 70 eV), m/z:** 275 ($M-C_2H_5O$), 247 ($M-C_3H_5O_2$), 228 ($M-C_7H_7$), 185 ($M-C_8H_7O_2$), 170 ($M-C_8H_8NO_2$), 96 ($C_5H_6NO$), 91 ($C_7H_7$).

**Example 3**

**(R,S)-5-Benzyloxycarbonylamino-2-oxo-1-pyrrolidineacetic acid**

To an ice cold solution of ethyl (R,S)-5-benzyloxycarbonyl-amino-2-oxo-1-pyrrolidineacetate (8.5 g) in methanol (64 ml), a solution of potassium hydroxide 85% (2 g) in methanol (43 ml), was added dropwise. The solution was stirred at room temperature for six hours, the solvent was removed under vacuum, the residue was dissolved in water and adjusted to pH 1 with 20% hydrochloric acid.

The precipitate was collected and dried to give 6.4 g of the title compound, as a white powder melting at 139-141°C.

**$^1$H-NMR (DMSO-$d_6$), delta:** 7.98 (bd, J = 9Hz, 1H, NH); 7.35 (s, 1H, Ph); 5.28 (c.a., 1H, CH); 5.06 (s, 2H, $\underline{CH_2}Ph$); 4.06 and 3.56 (ABq, J = 17Hz, 2H, $NH\underline{CH_2}O$); 2.50-1.80 (c.a., 4H, $CH_2CH_2$).

**MS (E.I., 70 eV), m/z:** 201 ($M-C_7H_7$), 157 ($M-C_8H_7O_2$), 151 ($C_8H_9NO$), 141 ($M-C_8H_9NO$), 108 ($C_7H_8O$), 96 ($C_5H_6NO$), 91 ($C_7H_7$).

**Example 4**

**Ethyl (R,S)-5-amino-2-oxo-1-pyrrolidineacetate**

A mixture of ethyl (R,S)-5-benzyloxycarbonylamino-2-oxo-

1-pyrrolidineacetate (3 g), ethanol (60 ml) and 10% palladium on carbon (0.3 g) was hydrogenated (20°C, ambient pressure) for one hour. The catalyst was filtered off and the solvent was evaporated to yield 1.4 g of the title compound as an oil, Rf = 0.25 (silica gel plates, ethyl acetate-acetone-methanol 6:3:1).

**$^1$H-NMR ($CDCl_3$), delta:** 4.60 (c.a., 1H, CH); 4.15 (q, J = 7Hz, 2H, $\underline{CH_2}CH_3$); 4.13 - 3.95 (ABq, J = 20Hz, 2H, $NCH_2CO$); 2.50-1.50 (c.a., 4H, $CH_2CH_2$); 1.80 (s, 2H, $NH_2$); 1.22 (t, J = 7Hz, 3H, $CH_2\underline{CH_3}$).

**MS (E.I., 70 eV), m/z:** 185 (M-H)+, 170 (M-$NH_2$), 141 (M-$C_2H_5O$), 113 (M-$C_3H_5O_2$), 99 (M-$C_4H_7O_2$), 84 ($C_4H_6NO$).

## Example 5

**(R,S)-5-Amino-2-oxo-1-pyrrolidineacetic acid hydrochloride**

A mixture of (R,S)-5-benzyloxycarbonylamino-2-oxo-1-pyrrolidine acetic acid (2.6 g), methanol (78 ml), 2N hydrochloric acid (4.5 ml) and 10% palladium on carbon (0.3 g) was hydrogenated (20°C, ambient pressure) for 30 minutes.

The catalyst was filtered off, the solvent was evaporated and the solid residue was triturated with diisopropyl ether to yield 1,3 g of the title compound as a white solid melting at 140-141°C.

**$^1$H-NMR (DMSO-$d_6$), delta:** 9.00 (bs, 4H, $NH_3$+COOH); 5.00 (c.a., 1H, CH); 4.15 (s, 2H, $NCH_2CO$); 2.90-2.00 (c.a., 4H, $CH_2CH_2$).

**MS (E.I., 70 eV), m/z:** 141 (M-$NH_3$), 123 (M-$H_2O$, $NH_3$), 96 ($C_5H_6NO$).

**Example 6**

**(R,S)-Dihydro-1-benzyloxycarbonyl-1H-pyrrolo[1,2-a]-imidazole-2,5(3H,6H)-dione**

A mixture of (R,S)-5-benzyloxycarbonylamino-2-oxo-1-pyrrolidineacetic acid (6.1 g), acetic anhydride (61 ml) and anhydrous sodium acetate (1.7 g) was refluxed for one hour. The solvent was evaporated under vacuum, the residue was triturated with water (50 ml) and collected, to give 4.4 g of the title compound melting at 110-111°C.

**$^1$H-NMR ($CDCl_3$), delta:** 7.40 (s, 5H, Ph); 5.60 (t; J = 6Hz, 1H, CH); 5.33 (s, 2H, $\underline{CH_2}Ph$); 4.35 and 3.66 (ABq, J = 17Hz, 2H, $NCH_2CO$); 3.00-1.90 (c.a., 4H, $CH_2CH_2$).

**MS (E.I., 70 eV), m/z:** 274 (M+.), 167 (M-$C_7H_6O$), 139 (M-$C_8H_7O_2$), 91 ($C_7H_7$), 84 ($C_4H_6NO$).

**Example 7**

**(R,S)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5-(3H,6H)-dione**

A mixture of (R,S)-dihydro-1-carbobenzyloxy-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione (4 g), methanol (120 ml) and 10% palladium on carbon (0.4 g), was hydrogenated (20°C, ambient pressure) for one hour. The catalyst was filtered off and the solvent was evapaorated under vacuum, to give the crude title compound as a solid, melting at 130-133°C. Crystallization from isopropyl alcohol gave 1.2 g of the pure title compound as a white powder, melting at 152-154°C.

**Example 8**

**(R,S)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione**

To a mixture of (R,S)-5-amino-2-oxo-1-pyrrolidineacetic acid hydrochloride (0.2 g), acetonitrile (60 ml) and triethylamine (0.1 g), a solution of

dicyclohexylcarbodiimide (0.2 g) in acetonitrile (8 ml) was added dropwise. The solution was stirred for 24 hours, the precipitate was filtered off and the solvent evaporated under vacuum. The solid residue was chromatographed over silica gel (ethyl acetate-acetone-methanol 6:3:1) to yield 80 mg of the title compound as a white solid, melting at 151-153°C.

**Example 9**

**(R,S)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione**

To a solution of ethyl (R,S)-5-amino-2-oxo-1-pyrrolidine-acetate (0.5 g) in anhydrous toluene (10 ml), potassium tert-butoxide (0.3 g) was added and stirring was continued for three hours. Then more potassium tert-butoxide (0.3 g) was added and after 1.5 hours the mixture was neutralized with 1N hydrochloric acid. The separated aqueous layer was passed through a column of cation exchanger Amberlite IR 120 (4 g) and evaporated. The residue was chromatographed over silica gel (ethyl acetate - acetone - methanol 6:3:1) to yield 80 mg of the title compound as a white solid, melting at 149-151°C.

**Example 10**

**(R,S)-Dihydro-1-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione**

To a solution of ethyl (R,S)-5-amino-2-oxo-1-pyrrolidineacetate (1 g) in anhydrous tetrahydrofuran (20 ml), 1.6 M butyllithium in n-hexane (3.4 ml) was added dropwise, keeping the temperature between -70 and -65°C. After one hour the temperature was allowed to rise to 0°C and the reaction mixture was neutralized with 1N hydrochloric acid. The mixture was evaporated under vacuum and the residue was chromatographed over silica gel (ethyl acetate - acetone - methanol 6:3:1) to yield 0.2 g of the title compound.

**Example 11**

**(R)-1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-2-pyrrolidinone**

A stirred suspension of N-benzyloxycarbonyl-D-pyroglutamic acid (25 g) in freshly distilled dry toluene (125 ml) was flushed with nitrogen and treated with diphenylphosphoryl azide (20.5 ml). The mixture was heated to 80°C, and keeping this temperature, a solution of triethylamine (13.1 ml) in toluene (62.5 ml) was added dropwise during 3 h. To the clear solution, benzyl alcohol (10.7 ml) in toluene (62.5 ml) was added quickly and the mixture was allowed to reach room temperature. The crystalline product precipitated on standing. After filtration it was washed thoroughly with cold toluene and dried under vacuum, affording the title compound (18.61 g) as a white solid, m.p. 149-152°C; [alpha]$^{20}$D = +31.2 (c=1, DMF).

**$^1$H-NMR ($CDCl_3$), delta:** 7.35 (s, 10H, Ph); 5.72 (c.a., 2H, CH-NH); 5.25 (s, 2H, $COOCH_2$); 5.07 (s, 2H, $NHCOO\underline{CH_2}$); 2.00-3.10 (c.a., 4H, $CH_2CH_2$).

**MS (E.I., 70 eV), m/z:** 368 (M+.), 277 (M-$C_7H_7$), 260 (M-$C_7H_8O$), 217 (M-$C_8H_9NO_2$), 127 ($C_{15}H_{15}NO_2$), 107 ($C_7H_7O$), 91 ($C_7H_7$), 84 ($C_4H_6NO$).

**Example 12**

**(R)-5-Amino-2-pyrrolidinone hydrochloride**

A solution of (R)-1-benzyloxycarbonyl-5-benzyloxycarbonyl-amino-2-pyrrolidinone (18.61 g,) in methanol/dioxane (4/1) (2.5 l) and 10% hydrochloric acid (22.3 ml) was hydrogenated (20°C, ambient pressure) over 10% Pd/C (2.05 g). The reaction was allowed to proceed for 0.5 h, then the catalyst was removed by suction filtration through a Celite pad. Evaporation of the filtrate afforded the title compound (6.8 g) as a yellow solid, [alpha]$^{20}$D = +11.8° (c=0.17, $H_2O$/dioxane = 1/1).

**$^1$H-NMR (DMSO-d6), delta:** 8.70 (bs, 3H, $NH_3$+); 8.33 (bs, 1H, CONH);

4.88 (bs, 1H, CH); 2.80-1.80 (c.a., 4H, $CH_2CH_2$).

**MS (E.I., 70 eV), m/z**: 100 (M+.), 84 ($M-NH_2$).

**Example 13**

**(S)-5-Benzyloxycarbonylamino-2-pyrrolidinone**

To an ice cold solution of (R)-5-amino-2-pyrrolidinone hydrochloride (6.7 g) in water (1.4 l), benzyl chloroformate (12 ml) and 0.5 N NaOH (82 ml) were added. The reaction mixture was stirred at 2-7°C for 1.5 h. Then, 0.5 N sodium hydroxide was added portionwise to maintain the pH between 7 and 9 while the mixture was allowed to warm to room temperature. After 2.5 h, more benzyl chloroformate (12 ml) was added quickly and stirring was continued for 2 hours at room temperature. The mixture was extracted with dichloromethane (500 ml x 3). The organic layer was dried ($Na_2SO_4$) and evaporated under reduced pressure. The oily residue was triturated with diisopropyl ether to afford 8.5 g of the title compound as a white solid, m.p. 127-129°C; [alpha]$^{20}$D = -79.6 (c=1, MeOH).

**$^1$H-NMR ($CDCl_3$), delta**: 7.35 (s, 5H, Ph); 6.50 (bs, 1H, CONH); 5.70 (bd, J = 7Hz, 1H, CHNHCO); 5.40 (c.a., 1H, CH); 5.15 (s, 2H, $CH_2$Ph); 2.75-1.75 (c.a., 4H, $CH_2CH_2$).

**MS (E.I., 70 eV), m/z**: 234 ($M^+$.), 190 ($M-CO_2$), 143 ($M-C_7H_7$), 126 ($M-C_7H_8O$), 108 ($C_7H_8O$), 91 ($C_7H_7$), 84 ($C_4H_6NO$).

**Example 14**

**Ethyl (R)-5-benzyloxycarbonylamino-2-oxo-1-pyrrolidineacetate**

The procedure of example 2 was repeated starting from (R)-5-benzyloxy-carbonylamino-2-pyrrolidinone (9.24 g) to afford the title compound (11.8 g) as an oil. Rf: 0.33 (silica gel plates, dichloromethane-methanol 95:5).

**$^1$H-NMR ($CDCl_3$), delta**: 7.35 (s, 5H, Ph); 5.85 (bd, J = 8.5HZ, 1H, NH);

5.50 (c.a., 1H, CH); 5.10 (2H, $\underline{CH_2}Ph$); 5.15 (q, J = 7.5Hz, 2H, $\underline{CH_2}CH_3$); 4.10 and 3.95 (ABq, J = 14Hz, 2H, $NCH_2CO$); 2.75-1.75 (c.a., 4H, $CH_2CH_2$); 1.22 (t, J = 7.5Hz, 3H, $CH_2\underline{CH_3}$).

**MS (E.I., 70 eV), m/z:** 320 ($M^+$.), 275 (M-$C_2H_5O$), 247 (M-$C_3H_5O_2$), 185 (M-$C_8H_7O_2$); 170 (M-$C_8H_8NO_2$), 91 ($C_7H_7$).

**Example 15**

**(R)-5-Benzyloxycarbonylamino-2-oxo-1-pyrrolidineacetic acid**

The procedure of example 3 was repeated starting from ethyl (R)-5-benzyloxycarbonylamino-2-oxo-1-pyrrolidineacetate (11.5 g) to afford the title compound (7.44 g) as a solid foam. Rf: 0.59, silica gel plates, butanol - acetic acid - water 4:1:1).

**$^1$H-NMR (DMSO-d6), delta:** 7.95 (bd, J = 9Hz, 1H, NH); 7.35 (s, 5H, Ph); 5.28 (c.a., 1H, CH); 5.06 (s, 2H, $\underline{CH_2}Ph$); 4.06 and 3.56 (ABq, J = 17 Hz, 2H, $NCH_2CO$); 2.50-1.80 (c.a., 4H, $CH_2CH_2$).

**MS (E.I., 70 eV), m/z:** 201 (M-$C_7H_7$), 151 ($C_8H_9NO_2$), 142 (M-$C_9H_{10}O_2$), 108 ($C_7H_{80}$), 91 ($C_7H_7$).

**Example 16**

**(S)-Dihydro-1-benzyloxycarbonyl-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione**

The procedure of example 6, was repeated starting from (R)-5-benzyloxy-carbonylamino-2-oxo-1-pyrrolidineacetic acid (7.33 g) to afford 4 g of the title compound as a brown solid, m.p. = 123-127°; [alpha]$^{20}$D = +53.8°, (c=1, DMF).

**$^1$H-NMR ($CDCl_3$), delta:** 7.40 (s, 5H, Ph); 5.60 (t; J = 6Hz, 1H, CH); 5.33 (s, 2H, $\underline{CH_2}Ph$); 4.40 and 3.70 (ABq, J = 17Hz, 2H, $NCH_2CO$); 3.00-1.90 (c.a., 4H, $CH_2CH_2$).

**MS (E.I., 70 eV), m/z:** 274 (M+.), 168 (M-$C_7H_6O$), 139 (M-$C_8H_7O_2$), 91 ($C_7H_7$), 84 ($C_4H_6NO$).

**Example 17**

**(R)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione**

The procedure of example 7, was repeated starting from (R)-dihydro-1-benzyloxycarbonyl-1H-pyrrolo[1,2-a]-imidazole-2,5[3H,6H]-dione (4 g) to afford the title compound (1.15 g) as a white solid, m.p. 197-200°;[alpha]$^{20}$D = -39.8°, (c=0.43, MeOH).

**$^1$H-NMR (DMSO-$d_6$), delta:** 8.68 (bs; 1H, NH); 5.25 (t, J = 4Hz, 1H, CH); 3.80 and 3.40 (ABq, J = 15Hz, 2H, $NCH_2CO$); 2.90-1.55 (c.a.; 4H, $CH_2CH_2$).

**MS (E.I., 70 eV), m/z:** 140 (M+.), 111 (M-CHO), 97 (M-CHNO); 84 ($C_3H_4N_2O$).

**Example 18**

**Benzyl (S)-5-carbethoxy-2-oxo-1-pyrrolidineacetate**

A mixture of ethyl L-pyroglutamate [E. Fischer et al., Berichte 44, 1333 (1911)] (13.1 g), tetrabutylammonium bromide (10.36 g) and potassium carbonate (45 g) in acetonitrile (100 ml) was stirred at 20°C for 1 hour. Benzyl 2-bromoacetate (25 ml) was added and the temperature was raised to 60°C. Stirring was continued for 2.5 hours, maintaining the temperature at 60-65°C. After cooling the insoluble material was filtered off and washed with diethyl ether.

The combined filtrates were evaporated under reduced pressure. The oily residue was dissolved in ethyl acetate (100 ml) and washed with 10% hydrochloric acid, a saturated solution of sodium hydrogen carbonate and water. The organic layer was dried and evaporated, the oily residue was

chromatographed over silica gel (eluting first with dichloromethane then with dichloromethane/methanol 8:2). The appropriate fractions were collected and evaporated to give 18.5 g of title compound as a brown oil; b.p. 240-250°C at 0.6 mmHg (partial decomposition); [alpha]$^{20}$D = -36.1°, (c=5; $CH_2Cl_2$).

**$^1$H-NMR ($CDCl_3$), delta:** 7.37 (s, 5H, Ph); 5.18 (s, 2H, $\underline{CH_2}Ph$); 4.70 and 3.84 (ABq, J = 17Hz, 2H, $NCH_2COO$); 4.45 (c.a., 1H, CH); 4.22 (q, J = 6Hz, 2H, $\underline{CH_2}CH_3$); 2.75-2.00 (c.a., 4H, $CH_2CH_2$); 1.28 (t, J = 6Hz, 3H, $CH_2\underline{CH_3}$).

**MS (E.I., 70 eV), m/z:** 305 (M+.), 232 (M-$C_3H_5O_2$), 214 (M-$C_7H_7$), 170 (M-$C_8H_7O_2$), 156 (M-$C_9H_9O_2$), 142 ($C_6H_8NO_3$), 98 ($C_5H_8NO$), 96 ($C_5H_6NO$), 91 ($C_7H_7$).

**Example 19**

**(S)-5-Carboethoxy-2-oxo-1-pyrrolidineacetic acid**

A mixture of benzyl (S)-5-carbethoxy-2-oxo-1-pyrrolidine-acetate (6.5 g, 21 mmol) and 10% Pd on charcoal (0.65 g) in ethyl acetate (65 ml) was hydrogenated at room temperature and ambient pressure. After 6 hours the catalyst was filtered off and the solvent was evaporated under vacuum, affording 4.6 g of the title compound as a yellowish oil, [alpha]$^{20}$D -36.1°, (c=5, $CH_2Cl_2$).
Dicyclohexylammonium salt: m.p.115°C.

**$^1$H-NMR ($CDCl_3$), delta:** 8.43 (bs, 1H, COOH); 4.65 and 3.87 (ABq, J = 18Hz, 2H, $NCH_2COO$); 4.48 (c.a., 1H, CH); 4.25 (q, J = 6Hz, 2H, $\underline{CH_2}CH_3$), 2.70-2.00 (c.a., 4H, $CH_2\underline{CH_2}$); 1.30 (t, J = 6Hz, 3H, $CH_2CH_3$).

**MS (E.I., 70 eV), m/z:** 215 (M+.), 197 (M-$H_2O$), 169 (M-$C_2H_6O$), 156 (M-$C_2H_3O_2$), 142 (M-$C_3H_5O_2$), 96 ($C_5H_6NO$).

**Example 20**

**(S)-5-Carbamoyl-2-oxo-1-pyrrolidineacetic acid**

A solution of (S)-5-carbethoxy-2-oxo-1-pyrrolidineacetic acid (22.1 g) in concentrated ammonia solution (170 ml) was stirred at room temperature for 3 h. After evaporation under vacuum, the oily residue was dissolved in water (150 ml) and stirred with cation exchange resin Amberlite IRA 120 (30 ml) for 2 hours. The resin was filtered off and the solution was evaporated under reduced pressure, affording the title compound (17.5 g) as a delequescent amorphous solid, [alpha]$^{20}$D = -14.5°, (c=5, $H_2O$). Dicyclohexylammonium salt: m.p. 187-190°C.

**$^1$H-NMR (DMSO-$d_6$)**, delta: 8.27 (bs, 1H, COOH); 7.92 and 7.15 (bs, 2H, $CONH_2$); 4.20 (c.a., 1H, CH); 4.10 and 3.35 (ABq, J = 17Hz, 2H, $NCH_2CO$); 2.40-1.70 (c.a., 4H, $CH_2CH_2$).

**MS (E.I., 70 eV), m/z**: 185 (M-H)+, 168 (M-$H_2O$), 142 (M-$CH_2NO$), 126 (M-$C_2H4O_2$), 96 ($C_5H_6NO$), 84 ($C_4H_6NO$).

**Example 21**

**(S)-5-Amino-2-oxo-1-pyrrolidineacetic acid hydrochloride**

A solution of (S)-5-carbamoyl-2-oxo-1-pyrrolidineacetic acid (14.7 g) and [bis(trifluoroacetoxy)iodo]benzene (34.5 g) in water (100 ml) and acetonitrile (200 ml) was stirred at room temperature, under nitrogen, for 4 hours. Acetonitrile was removed under reduced pressure, the aqueous layer was washed with diethyl ether (2 x 50 ml) and evaporated under reduced pressure. The residue was dissolved in 10% hydrochloric acid (50 ml) and evaporated. The residue was triturated with acetone to afford the title compound (7.5 g) as a white solid, m.p. > 250°C; [alpha]$^{20}$D = +2.5°, (c=1, water).

**$^1$H-NMR (DMSO-$d_6$), delta**: 9.75 (bs, 4H, $NH_3^+$ COOH); 5.00 (c.a., 1H, CH); 4.15 (s, 2H, $NCH_2CO$); 2.90-2.00 (c.a., 4H, $CH_2CH_2$).

**Example 22**

**(R)-Dihydro-1-benzyloxycarbonyl-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione**

A solution of (S)-5-carbamoyl-2-oxo-1-pyrrolidineacetic acid (1 g, 5.4 mmol) and [bis(trifluoroacetoxy)iodo]benzene (2.72 g, 6.2 mmol) in acetonitrile/water 1:1 (26 ml) was stirred at room temperature for 2.5 hours. Acetonitrile was added to obtain a clear solution and stirring was continued for 1.5 hours. The solution was evaporated, the residue was dissolved in water (20 ml) and washed with diethyl ether (2 x 15 ml). To the aqueous solution, sodium hydrogen carbonate (2.25 g) and benzyl chloroformate (1.9 ml) were added and the mixture was stirred at room temperature overnight. The solution was washed with dichloromethane (2 x 25 ml), acidified, and extracted with dichloromethane (2 x 25ml). Drying ($Na_2SO_4$) and evaporation of the organic solution afforded crude (S)-5-benzyloxycarbonylamino-2-oxo-1-pyrrolidineacetic acid (0.4 g). This compound was dissolved in acetic anhydride (5 ml) containing sodium acetate (150 mg) and the mixture refluxed for 1 hour. After evaporation the residue was triturated with water to yield 0.14 g of the title compound as a brown solid, m.p. 118-128°C [alpha]D = -52.2° (c=1, DMF).

**Example 23**

**(S)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione**

A mixture of (S)-5-amino-2-oxo-1-pyrrolidineacetic acid hydrochloride (7 g), triethylamine (5.05 ml) and dicyclohexylcarbodiimide (7.4 g) in acetonitrile (1 l) was stirred under nitrogen for 24 hours. The mixture was evaporated under reduced pressure, the residue was dissolved in water (50 ml), and the insoluble material filtered off. The aqueous filtrate was treated with cation exchanger Amberlite IRA 120 (40 ml) and anion exchanger Amberlite IR 68 (40 ml) under stirring for 1.5 hours . The resin was filtered off, the aqueous solution was evaporated under reduced pressure and the residue was triturated from isopropanol and recrystallized from isopropanol, to yield 1.5 g of the title compound as a white crystalline solid m.p. 197-202°C [alpha]$^{20}$D = +41.6°, (c=0.38,

MeOH).

**Example 24**

**(S)-Dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione**

The procedure of example 7 was reported starting from (S)-dihydro-1-benzyloxycarbonyl-1H-pyrrolo[1,2-a]imidazole-2, 5(3H,6H)-dione (0.14 g) to afford the title compound (0.03 g) as a white solid, m.p. 198-202°C; [alpha]$^{20}$D = +42.8°, (c=0.26, MeOH).

**Example 25**

**(R)-t-Butyl-5-carbomethoxy-2-oxo-1-pyrrolidineacetate**

A solution of (5-R)-methyl pyroglutamate (122g) in 1.75l of acetonitrile was cooled to 0°-5°C and 55-60% sodium hydride (34.1g) was added portionwise. Stirring was continued for 1.5 hours and t-butyl bromoacetate (175.5g) was added dropwise. The ice bath was removed and stirring continued for 1.5 hours. After evaporation of the solvent, the residue was dissolved in ethyl acetate, the organic phase was washed with a saturated solution of $NaHCO_3$, dried, and evaporated to dryness, to give the title compound (182.1g, 83%) as a yellow oil; [alpha]$^{20}$D = +42.3° (c = 5, $CH_2Cl_2$).

**$^1$H-NMR ($CDCl_3$), deltaH:** 4.53 - 3.60 (ABq, J = 17.5Hz, 2H, $NCH_2O$); 4.45 (m, 1H, NCHCO); 2.6 - 2.0 (m, 4H, $CH_2CH_2$); 1.45 (s, 9H, t-butyl).

**MS (E.I, 70 eV, 1.5 mA): m/z** 201(M-$C_4H_8$), 156 (M-$C_5H_9O_2$), 184 ($C_4H_9O$).

**Example 26**

**(S)-t-Butyl-5-carbomethoxy-2-oxo-1-pyrrolidineacetate**

The title compound was prepared using the same procedure described in Example 25 starting from (5-S)-methyl pyroglutamate; [alpha]$^{20}$D =-38.9 (c=5, $CH_2Cl_2$).

$^1$H-NMR ($CDCl_3$), delta$_H$: 4.53 - 3.50 (ABq, J = 17.5Hz, 2H, $NCH_2O$); 4.45 (m, 1H, NCHCO); 2.6 - 2.0 (m, 4H, $CH_2CH_2$); 1.45 (s, 9H, t-butyl)

MS (E.I., 70 eV, 1.5 mA): m/z 201 (M - $C_4H_8$), 156 (M - $C_5H_9O_2$), 184 ($C_4H_9O$).

**Example 27**

**(R)-t-Butyl-5-carbamoyl-2-oxo-1-pyrrolidineacetate**

A mixture of (5-R)-t-butyl-5-carbomethoxy-2-oxo-1- pyrrolidinacetate (182.1g) and 32% ammonium hydroxide (900 ml) was stirred at room temperature for 1.5 hours.

The excess of ammonia was removed under vacuum, the solution neutralised with 37% hydrochloric acid, and extracted with ethyl acetate. The organic phase was dried over sodium sulphate and evaporated to dryness to give the title compound 104.7 g (61.1%) as a white powder, m.p. 132-135°C; [alpha]$^{20}$D = + 32.4° (c = 5, $CH_2Cl_2$).

$^1$H-NMR (DMSO - db), delta$_H$: 7.55 - 7.12 (bs, 2H, $CONH_2$); 4.25 - 3.40 (ABq, J = 17.5Hz, 2H, $NCH_2CO$); 4.15 (m, 1H, NHCO); 2.40 - 1.75 (m, 4H, $CH_2CH_2$); 1.45 (s, 9H, t-butyl).

MS (E.I, 70 eV, 1.5 mA): m/z = 198 (M - $CNH_2O$), 185 (M - $C_4H_9$), 142 (M - $CNH_2O$ - $C_4H_8$).

**Example 28**

**(S)-t-Butyl-5-carbamoyl-2-oxo-1-pyrrolidineacetate**

The title compound was prepared using the same procedure described in Example 27 starting from (5-S)-t-butyl-5-carbomethoxy-2-oxo-1-pyrrolidinacetate; m.p. 128-129°C; [alpha]$^{20}$D= - 31.3° (c = 5, $CH_2Cl_2$).

**$^1$H-NMR (DMSO - db), deltaH:** 7.60 - 7.17 (bs, 2H, $CONH_2$); 4.25 - 3.40 (ABq, J = 17.5, 2H, $NCH_2CO$); 4.15 (m, 1H, NHCO); 2.40 - 1.75 (m, 4H, $CH_2CH_2$); 1.45 (s, 9H, t-butyl).

**MS (E.I, 70 eV, 1.5 mA): m/z** = 198 (M - $CNH_2O$), 185 (M - $C_4H_9$), 1.42 (M - $CNH_2O$ - $C_9H_8$).

**Example 29**

**(R)-5-Amino-2-oxo-1-pyrrolidineacetic acid, hydrochloride**

A solution of 5.7% sodiuim hypochlorite (570 ml) was added dropwise to a solution of sodium hydroxide pellets (51.9 g) in water (1.05 l), maintaining the temperature at 0 - 5°C. To this solution, (5-R)-t-butyl-5-carbamoyl-2-oxo-1-pyrrolidinacetate (104.7g), was added portionwise maintaining the same temperature, and then for 15 minutes at 55-60°C. After cooling to 0-5°C, 37% of hydrochloric acid (145 ml) was added to pH2. The solution was evaporated under vacuum and the residue triturated with methanol.

The solvent was removed to give the title compound (69.8 g, 83%) as a white solid; [alpha]$^{20}$D = -2,3° (c=1, $H_2O$)

**$^1$H-NMR (DMSO - db), deltaH:** 9.5 (bs, 1H, COOH); 4.95 (m, 1H, NCHCO); 4.15 (s, 2H, $NCH_2CO$); 2.85 - 2.0 (m, 4H, $CH_2CH_2$).

**MS (E.I., 70 eV, 1.5 mA): m/z** 141 (M - $NH_3$), 123 (M - $H_2O$, $NH_3$).

**Example 30**

**(S)-5-Amino-2-oxo-1-pyrrolidineacetic acid, hydrochloride**

The title compound was prepared using the same procedure described in Example 29, starting from (5-S)-t-butyl-5-carbamoyl-2-oxo-1-pyrrolidinacetate.

**Example 31**

**(S)-Dihydro-1-acetyl-1H-pyrrolo[1,2a]imidazole-2,5(3H, 6H)-dione**

A mixture of (5-R)-5-amino-2-oxo-1-pyrrolidinacetic acid hydrochloride (69.8g), anhydrous sodium acetate (29.4 g) and acetic anhydride (700 ml), was refluxed for 1.5 hours. The brown mixture was allowed to cool to room temperature and then evaporated to dryness.

The residue was treated under stirring with ethyl acetate and a saturated solution of ammonium sulphate.

The organic layer was dried over sodium sulphate and evaporated under vacuum to give the title compound (54g, 82.5%) as an oil; m.p. 82-83°C; $[alpha]^{20}D$ = + 159° (c = 0.1, MeOH)

**$^1H$-NMR ($CDCl_3$), delta$_H$:** = 5.65 (m, 1H, NCHN); 4.45 - 3.75 (ABq, J = 17.5Hz, 2H, $NCH_2CO$); 3.1 - 2.0 (m, 4H, $CH_2CH_2$); 2.50 (5, 3H, $COCH_3$).

**MS (E.I., 70 eV, 1.5 mA): m/z** = 154 (H - CO), 139 (H - $C_2H_3O$).

**Example 32**

**(R)-Dihydro-1-acetyl-1H-pyrrolo[1,2a]imidazole-2,5(3H,6H)-dione**

The title compound was prepared using the same procedure described in Example 31, starting from (5-S)-5-amino-2-oxo-1-pyrrolidinacetic acid hydrochloride; m.p. 81-82°C, $[alpha]^{20}D$ = - 153.9° (c = 0.1, MeOH).

**$^1$H-NMR ($CDCl_3$), delta$_H$:** 5.65 (m, 1H, NCHN); 4.615 - 3.75 (ABq, J = 17.5Hz, 2H, $NCH_2CO$); 3.1 - 2.0 (m, 4H, $CH_2CH_2$); 2.50 (s, 3H, $COCH_3$).

**MS (E.I., 70 eV, 1.5 mA): m/z** = 154 (H - CO), 139 (H - $C_2H_3O$).

**Example 33**

**(R)-Dihydro-1H-pyrrolo[1,2a]imidazole-2,5(3H,6H)-dione**

A mixture of (7a-S)-dihydro-1-acetyl-1H-pyrrolo[1,2a] imidazole-2,5-(3H, 6H)-dione (54 g), Amberlite IR 120 (54 g) in water (540 ml), was stirred at room temperature for 24 hours. The resin was collected on a Buckner funnel and the dark filtrate was evaporated under vacuum, the residue was triturated with isopropanol to give the title compound.

Crystallisation from isoproponal gave the pure compound (15.5 g) as a white crystalline solid, m.p. 197-199°C, [alpha]$^{20}$D = - 39.2° (c = 1, MeOH).

**$^1$H-NMR ($DMSOd_6$) delta$_H$:** 8.63 (bs, 1H, NH); 5.23 (t, J = 5Hz, 1H, $CH_2\underline{CH}$); 3.8 - 3.45 (ABq, J = 17 Hz, 2H, $NCH_2CO$); 2.90 - 1.60 (m, 4H, $CH_2CH_2$).

**MS (E.I., 70 eV, 1.5 mA): m/z** = 140 ($M^+$), 97 (M - CONH).

**Example 34**

**(S)-Dihydro-1H-pyrrolo[1,2a]imidazole-2,5(3H,6H)-dione**

The title compound was prepared using the same procedure described in Example 33 starting from (R)-dihydro-1-acetyl-1H-pyrrolo[1,2a]imidazole-2,5-(3H,6H)-dione; m.p. 197-199°C, [alpha]$^{20}$D = + 39.9° (c = 1, MeOH)

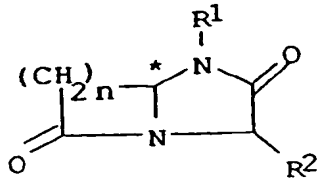
**$^1$H-NMR ($DMSOd_6$) delta$_H$:** 8.63 (bs, 1H, NH); 5.23 (t, J = 5Hz, 1H, $CH_2\underline{CH}$); 3.8 - 3.45 (ABq, J = 17Hz, 2H, $NCH_2CO$); 2.90 - 1.60 (m, 4H,

$CH_2CH_2$).

**MS (E.I, 70 eV, 1.5 mA): m/z** = 140 (M+), 97 (M - CONH).

## Claims

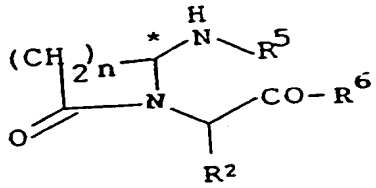
1. A process for the preparation of compounds of formula (I):



(I)

wherein
$R^1$ represents hydrogen, $C_{1-4}$ alkyl, $CHR^3CONHR^4$ or $CHR^3COOR^4$ in which $R^3$ and $R^4$ each independently represent hydrogen or $C_{1-4}$ alkyl;
$R^2$ represents hydrogen or $C_{1-5}$ alkyl; and n is an integer 2, 3 or 4;

which process comprises cyclising a compound of formula (II):



(II)

wherein $R^2$ and n are as defined in relation to formula (I);
$R^5$ represents hydrogen or a group $COOR^7$ wherein $R^7$ is a $C_{1-4}$ alkyl group or a benzyl group; and $R^6$ represents a hydroxy group or a group $OR^8$ wherein $R^8$ represents $C_{1-6}$ alkyl or a benzyl group; and thereafter, as necessary, carrying out one or more of the following steps:

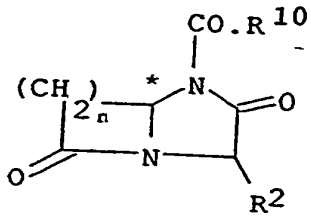
i) removing any protecting group; and

ii) converting a compound of formula (I) into another compound of formula (I).

2. A process according to claim 1, wherein the cyclisation is effected by a cyclising reagent.

3. A process according to claim 1 or claim 2, wherein the cyclising reagent is a carboxylic anhydride.

4. A process according to claim 3, wherein the cyclisation of the compound of formula (II) provides a compound of formula (III):



(III)

wherein $R^2$ and n are as defined in relation to formula (I) and $R^{10}$ is a $C_{1-6}$ alkyl group or a group $OR^7$ wherein $R^7$ is as defined in relation to formula (II); and wherein the compound of formula (III) is converted into a compound of formula (I), wherein $R^1$ is H, by hydrogenolysis or hydrolysis, the resulting compound of formula (I) subsequently being converted into other compounds of formula (I) as desired.

5. A process according to claim 1, wherein $R^6$ is OH and the cyclisation of a compound of formula (II) is effected under dehydration cyclisation conditions in the presence of a dehydration cyclisation reagent.

6. A process according to claim 5, wherein the dehydration cyclisation reagents include dicyclohexylcarbodiimide or carboxylic anhydrides such as acetic anhydride.

7. A process according to claim 1, wherein $R_6$ is a group $OR_8$ and the cyclisation is effected by use of a strong base such as n-butyl lithium or potassium t-butoxide.

8. A process according to claim 1, for the preparation of a resolved form ((R) or (S)) isomer of a compound of formula (I) which process comprises the sequence of reactions summarised below in Schemes 1 to 5:

**Scheme (1):**

(II) → (I)

**Scheme (2):**

(II) → (III) → (I)

**Scheme (3):**

(VII) → (VI) → (IV) → (II) → (I)

**Scheme (4):**

(VII) → (VI) → (IV) → (II) → (III) → (I)

**Scheme (5):**

(X) → (IX) → (II) → (II) → (I)

and wherein the compounds of formulae (I), (II), (III), (IV), (VI), (VII), (IX) and (X) are as defined above and the reaction conditions for each reaction are as defined hereinbefore.

9. A process according to schemes (1) and (3) of claim 8, wherein the cyclisation of (II) to (I) is effected using dicyclohexylcarbodiimide.

10. A process according to schemes (2), (4) and (5) of claim 8, wherein the cyclisation of (II) to (III) is effected using a carboxylic anhydride.

11. A process according to scheme (4) of claim 8, wherein variable $R^6$ in the compounds of formulae (VI) and (IV) is -O-t-butyl.

12. A process according to claim 1, for the preparation of a compound selected from the list consisting of:

(R,S)-dihydro-1H-pyrrolo[1,2-a]imidazole-2,5-(3H,6H)-dione;

(R)-dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione;and

(S)-dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-dione.

5

International Application No

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/04; C07D471/04; //(C07D487/04,235:00,209:00) (C07D471/04,235:00,221:00)(C07D487/04,235:00,223:00)

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | C07D |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No.[13] |
|---|---|---|
| A | EP,A,0 335 483 (ISF) 4 October 1989 cited in the application see claim 4 ----- | 1 |

° Special categories of cited documents : [10]

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## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 11 FEBRUARY 1993 | 26.02.93 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | ALFARO FAUS I. |

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# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9202560
SA 66848

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 11/02/93
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